Thieme Chemistry Journal Awardees - Where are They Now? Regio- and Stereoselective Radical Additions of Thiols to Ynamides

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CITATION:

Sato, Akinori ...[et al]. Thieme Chemistry Journal Awardees - Where are They Now? Regio- and Stereoselective Radical Additions of Thiols to Ynamides. Synlett 2009, 2009(1): 28-31

ISSUE DATE:

2009-01

URL:

http://hdl.handle.net/2433/123414

Regio- and Stereoselective Radical Additions of Thiols to Ynamides

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Abstract: Regioselective and stereoselective radical additions of arenethiols to various ynamides have been developed. Mixing ynamides and arenethiols in the presence of a catalytic amount of triethylborane affords the corresponding adducts, (*Z*)-1-amino-2-thio-1-alkenes, in excellent yields with high selectivities. The products can be reduced by means of trifluoroacetic acid and triethylsilane to yield 1-amino-2-thioalkanes.

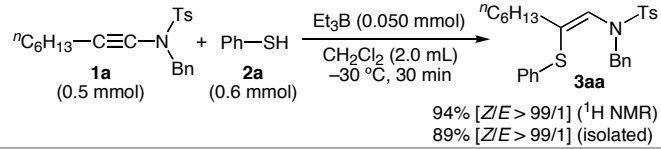
Key words: Radical, Hydrothiolation, Ynamide, Hydrogenation

Because of the high importance of organosulfur compounds, development of new reactions to introduce sulfur atoms to organic molecules is indispensable.[1] Radical addition of thiols to unsaturated bonds is one of the most basic and concise methods to achieve the purpose.[2,3] Although radical additions of thiols to terminal alkynes are well-known, examples of additions to internal alkynes are limited.[2c,4] Furthermore, additions to heteroatom-substituted internal alkynes have scarcely been reported.[5]

We have focused on *N*-alkynylamides (ynamides),[6] as heteroatom-substituted internal alkynes in the radical addition reaction. Here we report radical hydrothiolation of ynamides,[7,8] which yields synthetically useful (*Z*)-1-amino-2-thio-1-alkene derivatives[9] regio- and stereoselectively.[10]

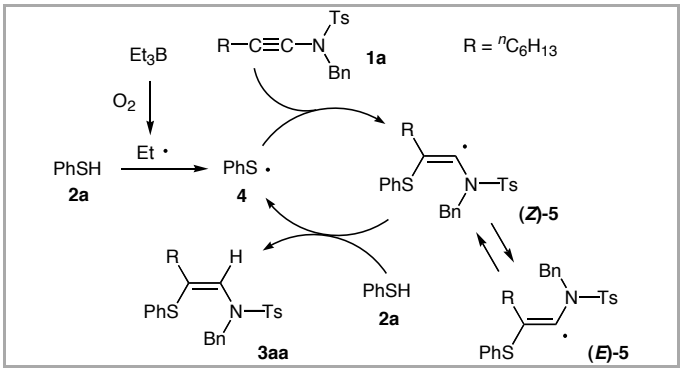
Under air, a catalytic amount of triethylborane[11] was added to a solution of *N*-benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide[12] (**1a**) and benzenethiol (**2a**, 1.2 equiv) in dichloromethane at –30 ºC. After the mixture was stirred for 30 min at the same temperature, the mixture was concentrated. NMR analysis of the crude mixture indicated the formation of *N*-benzyl-*N*-(2-phenylthio-1-octenyl)-*p*-toluenesulfonamide (**3aa**, 94%, *Z*/*E* > 99/1). We confirmed by NOE experiments that the *Z* isomer was exclusively formed. Silica gel column chromatography afforded **3aa** in 89% yield (Scheme 1).[13]

Scheme 1. Triethylborane-initiated Hydrothiolation of Ynamide **1a**.



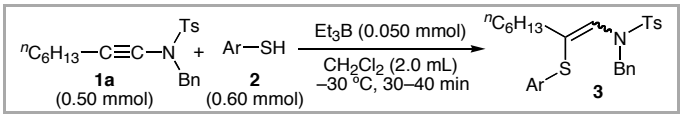
This reaction would proceed as follows (Scheme 2). Initially, an ethyl radical, generated from triethylborane with a trace amount of molecular oxygen, abstracts hydrogen atom from benzenethiol to form thiyl radical **4**. The electron-deficient radical[14] immediately reacts with ynamide **1a**, an electron-rich alkyne, to furnish vinyl radical **5**. The carbon–sulfur bond formation occurs regioselectively at the 2-position of ynamide **1a**, where the higher electron density resides. The *Z* isomer of vinyl radical **5** selectively abstracts hydrogen atom from benzenethiol.[15] Product **3aa** is thus formed, and thiyl radical **4** is regenerated to complete the radical chain.

Scheme 2. Plausible Reaction Mechanism.



Electron-deficient arenethiol participated smoothly in this radical reaction (Table 1, entries 2 and 3). On the other hand, additions of electron-rich arenethiols were not efficient (entries 4–6). These poor yields would be due to the low reactivity of the electrophilic thiyl radicals that are stabilized by electron-donating aryl groups. Addition of a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to the reaction system or the absence of triethylborane almost prevented the reaction (entries 7 and 8). These results strongly support that the reaction would proceed via the radical chain mechanism.

Table 1. Hydrothiolation of **1a** with Various Arenethiols.



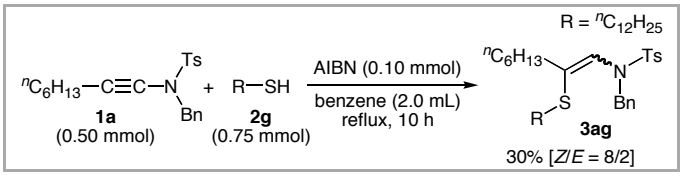
entry	Ar	product	isolated yield /% [*Z*/*E*]
1	Ph (**2a**)	**3aa**	89 [> 99/1]
2	*p*-Br-C_6H_4 (**2b**)	**3ab**	88 [> 99/1]

3	C_6F_5 (**2c**)	**3ac**	93 [> 99/1]
4	*o*-Me-C_6H_4 (**2d**)	**3ad**	31[d] [N.D.[e]]
5	*p*-Me-C_6H_4 (**2e**)	**3ae**	23[d] [N.D.[e]]
6[a]	*p*-MeO-C_6H_4 (**2f**)	**3af**	35 [> 99/1]
7[b]	Ph (**2a**)	**3aa**	6[d] [59/41]
8[c]	Ph (**2a**)	**3aa**	<2[d] [N.D.[e]]

[a] The reaction was performed at room temperature. [b] With TEMPO (0.10 mmol). [c] Without triethylborane. [d] NMR yield. [e] Not determined.

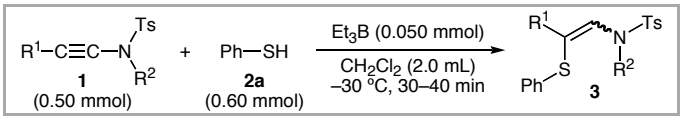
The addition of dodecanethiol (**2g**) to ynamide **1a** did not proceed at –30 ºC. The reaction in boiling benzene with AIBN [2,2'-azobis(isobutyronitrile)] instead of Et_3B proceeded, although the yield and stereoselectivity were unsatisfactory (Scheme 3).

Scheme 3. Hydrothiolation of **1a** with Dodecanethiol.



A wide range of ynamides were subjected to the radical addition of benzenethiol (**2a**) (Table 2). Not only **1a** but also ynamides bearing an acid-sensitive THP ether moiety and a base-sensitive ester moiety underwent the addition reactions without loss of the functional groups (entries 2 and 3). Benzenethiol added to ynamide **1d** substituted by a secondary alkyl group in lower yield with slightly lower selectivity (entry 4). Ynamide **1e** having a tertiary alkyl group resisted the addition reaction (entry 5).[16] Replacement of the benzyl group of **1a** by a methyl group slightly decreased the regioselectivity of the reaction (entry 1 vs. entry 6). The allyl group of **1g** remained unchanged under the reaction conditions (entry 7). *N*-Phenyl ynamide **1h** was less reactive than the *N*-benzyl analogue **1a** (entry 8). Not only *p*-toluenesulfonamides **1a–1h** but also camphorsulfonamides **1i** and **1j** and Boc-protected ynamide **1k** underwent the radical addition smoothly (Scheme 4).

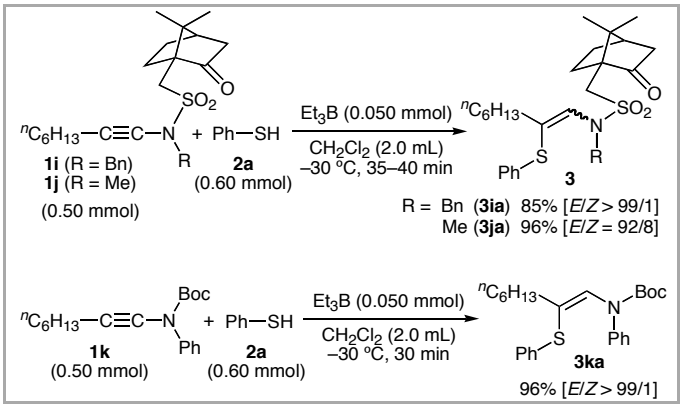
Table 2. Radical Hydrothiolation of *p*-Toluenesulfonyl-substituted Ynamides with Benzenethiol..



entry	R^1	R^2	**1**	product	isolated yield /% [*Z*/*E*]
1	$^nC_6H_{13}$	Bn	**1a**	**3aa**	89 [> 99/1]
2	$THPOCH_2$	Bn	**1b**	**3ba**	90 [> 99/1]
3	$EtO_2C(CH_2)_4$	Bn	**1c**	**3ca**	97 [> 99/1]
4	$^cC_6H_{11}$	Bn	**1d**	**3da**	73 [97/3]
5	^tBu	Bn	**1e**	**3ea**	15 [N.D.[a]][b]
6	$^nC_6H_{13}$	Me	**1f**	**3fa**	97 [96/4]
7	$^nC_6H_{13}$	allyl	**1g**	**3ga**	84 [> 99/1]
8	$^nC_6H_{13}$	Ph	**1h**	**3ha**	60 [> 99/1]

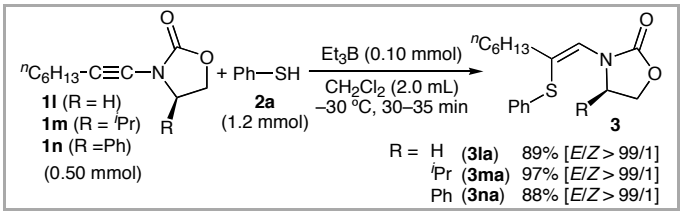
[a] Not determined. [b] NMR yield.

Scheme 4. Radical Hydrothiolation of Various Ynamides with Benzenethiol.



The addition reactions to *N*-(1-alkynyl)oxazolidinones led to the exclusive formation of the corresponding *Z* adducts in excellent yields (Scheme 5). In these cases, 2.4 equiv of benzenethiol and a larger amount of triethylborane were needed.

Scheme 5. Radical Hydrothiolation of *N*-(1-Alkynyl)oxazolidinone with Benzenthiol.

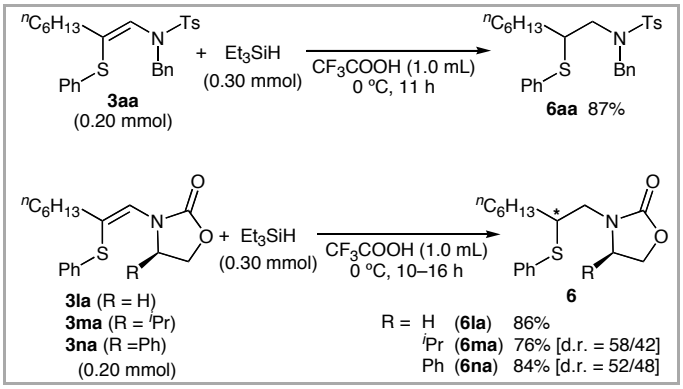


Hydrogenation of the double bonds of adducts **3** could provide interesting structures having a phenylthiolated chiral center. We hence examined to reduce alkenylamides **3**. Many attempts to reduce the double of **3aa** in the presence of various transition metal complexes under hydrogen atmosphere resulted in failure, suffuring from no conversions.

On the other hand, treatment of **3aa** with triethylsilane in trifluoroacetic acid reduced the alkene moiety[17] to afford desired *N*-(2-phenylthioalkyl)amides **6aa** in good yield (Scheme 6).[18] Unfortunately, attempted diastereoselective reduction of chiral *N*-(1-alkenyl)oxazolidinones **3ma** and **3na** resulted in the formation of 1:1 mixtures of diastereomers. However, the diastereomers were separable from each other by flash column chromatography on silica gel.

In summary, we have developed a concise method to synthesize (*Z*)-1-amino-2-thio-1-alkene derivatives in high yields with excellent regio- and stereoselectivity. The products can be hydrogenated by the action of triethylsilane in trifluoroacetic acid. Since reduced products **6** have asymmetric carbons, they can be useful as chiral building blocks[19] and chiral bidentate *N*,*S*-ligands of transition metal catalysts.[20]

Scheme 6. Reduction of Double Bonds of Adducts **3**.



Acknowledgement

This work was supported by Grants-in-Aid for Scientific Research and GCOE Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. A.S. acknowledges JSPS for financial support.

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(13) **General experimental procedure for radical hydrothiolation of ynamides:** Under air, triethylborane (1.0 M hexane solution, 0.050 mL, 0.050 mmol) was added to a solution of *N*-benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide (**1a**, 0.18 g, 0.50 mmol) and benzenethiol (**2a**, 0.062 mL, 0.60 mmol) in dichloromethane (2.0 mL) at –30 ºC. The solution was stirred for 30 min at the same temperature and concentrated in vacuo. ^{1}H NMR analysis of the crude mixture showed a 94% yield of the adduct (*Z*/*E* > 99/1). Silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) afforded *N*-benzyl-*N*-[(*Z*)-2-phenylthio-1-octenyl]-*p*-toluenesulfonamide (**3aa**) as a white solid in 89% yield (0.21 g, 0.45 mmol).
3aa: IR (Nujol) 2925, 1456, 1351, 1339, 1161, 1089, 1024, 741, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 7.5 Hz, 3H), 1.02–1.15 (m, 4H), 1.16–1.35 (m, 4H), 1.89 (t, *J* = 7.0 Hz,

2H), 2.45 (s, 3H), 4.46 (s, 2H), 5.64 (s, 1H), 6.90–6.94 (m, 2H), 7.13–7.21 (m, 3H), 7.26–7.35 (m, 5H), 7.36–7.41 (m, 2H), 7.76–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.04, 21.57, 22.50, 28.09, 28.25, 31.40, 33.36, 54.15, 124.26, 127.14, 127.62, 127.67, 128.32, 128.58, 128.77, 129.60, 132.31, 133.10, 135.63, 135.83, 142.86, 143.59. Found: C, 70.00; H, 6.94%. Calcd for $C_{28}H_{33}NO_2S_2$: C, 70.11; H, 6.93%.

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(15) The diastereoselectivity can be explained by steric effect. In reference 4b, Montevecci and Spagnolo insisted that primary alkyl groups are bulkier than a phenylthio group. We thus assume that vinyl radical **5** would exist almost as a Z form to prevent the steric repulsion between the bulky amide moiety and the alkyl group. The Z form abstract hydrogen from benzenethiol selectively. On the other hand, Montevecci et al. also insisted that a methyl group is smaller than a phenylthio group. Indeed, the reaction of *N*-methyl-*N*-(1-propenyl)-*p*-toluenesulfonamide with benzenethiol resulted in favorable formation of the corresponding Z adduct (E/Z = 2:3).

(16) The addition reaction of phenyl-substituted ynamide PhC≡CNTs(Bn) led to a mixture of stereo- and regioisomers.

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(18) **General experimental procedure for hydrogenations of the double bonds of enamides:** Under argon atmosphere, triethylsilane (0.048 mL, 0.30 mmol) was added to a solution of **3aa** (0.096 g, 0.20 mmol) in trifluoroacetic acid (1.0 mL, 13.5 mmol) at 0 ºC. The solution was stirred for 11 h at the same temperature. Then the reaction was quenched with a saturated $NaHCO_3$ solution and extracted with ethyl acetate (10 mL × 2). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography (hexane/ethyl acetate = 20/1) afforded *N*-benzyl-*N*-[2-(phenylthio)octyl]-*p*-toluenesulfonamide (**6aa**) as a colorless oil in 87% yield (0.084 g, 0.17 mmol).
6aa: IR (neat) 2926, 2855, 1599, 1456, 1439, 1342, 1162, 1092, 737, 654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.02–1.31 (m, 8H), 1.34–1.46 (m, 1H), 1.65–1.75 (m, 1H), 2.42 (s, 3H), 2.95–3.05 (m, 2H), 3.26–3.34 (m, 1H), 4.05 (d, *J* = 14.5 Hz, 1H), 4.31 (d, *J* = 14.5 Hz, 1H), 7.17–7.32 (m, 12H), 7.57–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.07, 21.49, 22.58, 26.62, 28.94, 30.82, 31.64, 47.40, 53.96, 54.26, 126.75, 127.30, 127.96, 128.58, 128.62, 128.83, 129.69, 131.62, 134.66, 135.82, 136.21, 143.37. Found: C, 70.03 H, 7.38%. Calcd for $C_{28}H_{35}NO_2S_2$: C, 69.81; H, 7.32%.

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